

# Paradoxical Effect of Hyperoncotic Albumin in Acutely Burned Children

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Hyperoncotic albumin proved ineffective as a plasma volume expander in the resuscitation of four acutely burned children. Hypovolemia and pulmonary edema were apparently intensified by an obligatory fluid shift following tissue extravasation of protein. We conclude that, when used, hyperoncotic albumin should be suspended in a sufficient volume of saline to produce a solution isotonic and iso-oncotic relative to plasma.

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Various formulae with and without colloids are used as planning guides for fluid resuscitation of burned patients, and by the end of the first 48 postburn hours, there may be considerable variation in the total volume and total sodium administered (11). In the final analysis, the fluid requirement as predicted by any formula is modified by the adequacy of the patient's urinary output and other physiologic indices, and the patient may receive other than the volume estimated. That the burn formula provides a close approximation of the total fluid volume actually needed to establish a satisfactory patient response is seen by the extremely close linear correlation of the amount of fluid required with burn size (13). The colloid component of the various formulae includes blood, dextran, plasma and plasma protein derivatives, and albumin. All of these solutions are administered on a volume-for-volume basis as predicted by the formulae, and all contain electrolytes in concentrations approximating normal serum values. During a 36-month period, four small children were referred to our institution after receiving large quantities of salt-poor 25% albumin as the colloid portion of their initial resuscitation. All four died early in the postburn period following the occurrence of refractory oliguria. In each of the four cases, the use of hyperoncotic albumin seems to have been a major factor related to the early mortality. No other pediatric patients with burns of comparable size developed hypovolemia and pulmonary symptoms.

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## PATIENTS

The records of all pediatric burn patients under the age of 4 years treated at the United States Army Institute of Surgical Research over a 36-month interval were reviewed. Large quantities of salt-poor hyperoncotic albumin were used in the initial resuscitation of four patients (Table I). The remainder of the pediatric patients (88) were treated with 5% solutions of colloid in salt-containing fluid based on the original Brooke formula.

## CASE REPORTS

**Case 1.** A 16-month-old, 12-kilogram female fell into a tub of hot water, sustaining a 60% total body surface burn. She was taken to a local hospital where her burns were debrided and she was begun on intravenous fluids. During the first 24 hours, she received approximately 1,800 ml of fluids, including 400 ml of 25% salt-poor albumin. Her volume requirement as predicted by the original Brooke formula was 2,900 ml. The amount of albumin given was assumed by the initial physician to be equivalent to five times that amount of plasma, as stated by the package insert for the hyperoncotic albumin. Initially, the infant's urine output was adequate, but by 18 hours following injury, the output had fallen to minimal levels. Mannitol was administered intravenously with only a limited response. Central venous pressure was 0 cm H<sub>2</sub>O. At the end of the first 24 postburn hours, the patient became anuric, failing to respond to additional fluid volume and furosemide. Her blood urea nitrogen at this time was 49 mg/dl. On the following day, the child became acidotic and sustained a cardiac arrest unresponsive to resuscitative measures. Acute tubular necrosis of the kidneys was found at autopsy.

**Case 2.** A 20-month-old, 14-kilogram male infant sustained a 53% total body surface burn when he fell into a tub of hot water. At a local hospital, a urethral catheter was inserted and intravenous fluids were begun. Over the first 24 hours following injury, the patient received 1,700 ml of dextrose in half-strength physiologic saline and 200 ml of 25% albumin. The patient's predicted volume requirement was approximately 3,100 ml of

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TABLE 1  
Fluid and colloid administration utilized for initial resuscitation

Patient	Weight (kg)	Volume Predicted* (ml)	Volume Given (ml)	Colloid Given† (gm)
1	12	2,880	1,880	100.0
2	14	3,165	1,890	50.0
3	9	1,440	1,260	25.0
4	10	2,600	2,550	112.5

\* Predicted by original Brooke formula for children.

† As 25% salt-poor albumin.

fluids. The 200 ml of hyperoncotic albumin was considered to be the equivalent of 1,000 ml of plasma. Urine output rapidly fell to less than 5 ml per hour. At this point, the patient was referred to our institution. On physical examination, he was found to be hypovolemic and in shock. His arterial pH was 7.18, and his blood urea nitrogen was 43 mg/dl. The patient was given an increased volume of fluid and sodium bicarbonate, and the central venous pressure rose from 0 to 10 cm H<sub>2</sub>O. However, urine output increased only minimally, and the acidosis persisted. Thirty-six hours postburn, the patient suffered the first of a series of cardiac arrests. He remained anuric and died 3 days following injury. Severe renal cortical necrosis was found at autopsy.

**Comment.** Both children died with shock arising from under-resuscitation. In each example, the quantity of fluid given was based in part on the assumption that a given volume of hyperoncotic albumin was equivalent to five times that volume of plasma. It appears that hyperoncotic albumin in these acutely burned patients is not a particularly effective plasma expander and that, at best, it may serve only as a replacement fluid on a volume-for-volume basis. As a result, these patients received 35% and 40% less fluid than would have been predicted to be necessary by the burn resuscitation fluid formula. Furthermore, these patients' intravenous fluids were markedly deficient in sodium, a major component of any resuscitation regimen. The administration of salt-poor albumin did little to improve this deficit. Because of these two factors, the above patients received less than the required volume and sodium needed for adequate resuscitation. This was further compounded in the second case by a moderate underestimation of total water requirements.

**Case 3.** A 7-month-old, 9-kilogram female sustained a 20% total body surface burn when she pulled a pot of hot coffee onto herself. At the hospital, the patient was begun on intravenous fluids; however, no urethral catheter was placed. Urine output was monitored only by frequency of voiding. During the first 24 hours, she received approximately 1,300 ml of fluid, including 100 ml of 25% albumin. Her predicted volume requirement was 1,400 ml. It was recorded that she voided 12 times during the first 24 hours after her burn but that the interval between voidings was increasing. At the end of the first day, her serum potassium was found to be 8.5 mEq/L and her blood urea nitrogen 48 mg/dl. The hyperkalemia was treated with glucose, insulin, and sodium bicarbonate. A urethral catheter was inserted, and output was recorded at 1 ml per hour. After 36 hours, her serum potassium was 7.0 mEq/L and her blood urea

nitrogen 55 mg/dl. Volume loading, mannitol, and furosemide had no effect on urine output. A central venous pressure catheter was placed and recorded a pressure of 34 cm of water. Physical examination and a chest X-ray were indicative of pulmonary edema, and the patient rapidly developed refractory hypotension. Intubation was required to control her severe respiratory acidosis; but within a few hours, she suffered a cardiac arrest and died. Acute tubular necrosis and severe pulmonary edema were found at autopsy.

**Case 4.** The last patient was a 2-year-old, 10-kilogram male infant who sustained a 70% total body surface burn when he climbed into a tub of hot water. A urethral catheter was placed, and intravenous fluid therapy based on a predicted requirement of 2,600 ml was promptly instituted. At the end of 14 hours, the patient had received 1,450 ml of fluid, including 200 ml of hyperoncotic albumin. However, only 40 ml of urine had been produced, and the patient was given an additional 100 ml of hyperoncotic albumin. After a brief rise to 30 ml for the following hour, urine output then fell to zero, in spite of continuing fluid loading. By the end of 24 hours, the patient had received 2,550 ml of fluid, including 450 ml of salt-poor hyperoncotic albumin. At this point, the patient became profoundly hypotensive and suffered a cardiac arrest, from which he could not be resuscitated. Acute tubular necrosis of the kidneys and interstitial pulmonary edema were found at autopsy.

**Comment.** Both of these patients received the amount of fluid predicted for a satisfactory resuscitation. In addition, they received more than adequate sodium loads. If volume and sodium administered are evaluated together, it would seem that these children actually received substantially more fluid than they should have required (10). The only unusual feature of these children's therapy was the excessive use of hyperoncotic albumin, with each child receiving an amount approximating 55% and 225% of his total body albumin, respectively. Each child developed a clinical picture of hypovolemia, in spite of receiving more than the calculated amount of resuscitation fluid. It seems that the hyperoncotic albumin was not only an ineffective resuscitation solution but actually may have accentuated the hypovolemia and contributed to the development of pulmonary edema.

## DISCUSSION

Within minutes after burn injury, a rapid shift of fluid and osmotically active proteins into damaged tissues begins to take place. Initially, more fluid than protein is lost, with a huge intravascular shift of water flowing across an osmotic pressure gradient created by the effects of thermal injury (2). After a few hours, changes in capillary membrane permeability begin to play an increasingly important role (7). Substances with molecular weights as high as 125,000 have been found to pass freely through the injured capillary membrane (14). In a much less severe fashion, capillary permeability is altered even in the unburned areas, resulting in an additional shift of fluids and protein as fluid infusion proceeds (1).

Certainly, the most important protein component lost into the injured tissues is albumin (6, 8). The rate at which albumin leaves the intravascular space triples, and

in patients with serious burns, more than 95% of injected labeled albumin disappears from the intravascular space in the first 36 hours (3). Approximately 25% is lost through the burned skin, while the remaining 70% is trapped in the extravascular space (3, 4). Initially, there is a less marked but significant increase in the rate of return of albumin to the blood by lymph channels; but after a few hours, this route begins to slow as the lymphatic vessels become blocked with coagulated fibrinogen (1, 3). Albumin and other proteins are trapped in the interstitial tissue, producing an increase in tissue colloid osmotic pressure and an augmented fluid flow into the extravascular space. Eventually, the static pressure of the inelastic burn eschar limits further fluid loss.

Albumin and other colloids are often used in the resuscitation of patients with acute burns, but the value of these components is not established. A wide variety of substances has been used, including various gelatins, dextrans, blood, and plasma, and results suggest that success is best correlated with the volume of fluid and quantity of sodium administered. Comparison of colloids containing sodium with those not containing sodium indicated the superiority of sodium-containing solutions (9). Furthermore, the efficacy of the sodium-free colloid solutions was found to be a function of their actual fluid volume (5). More recent studies suggest that sodium content is the most potent factor in fluid resuscitation, with the effect of 1 mEq of sodium equivalent to that of 13 ml of salt-free fluid volume in increasing cardiac output (10). Moreover, during the first 24 hours postburn the ability of any particular solution to expand plasma volume is dependent only on the rate of administration of that solution, whether it be electrolyte or colloid (12). The question of whether correction of blood volume is more important than restoration of fluid and sodium deficiencies in the burned and unburned peripheral tissue has not been answered, but in either case it appears that colloids, including albumin, are of no greater benefit than an equal volume of electrolyte-containing fluid.

Early investigations of the use of albumin as a substitute for blood established it as an effective plasma expander in normal and wounded soldiers. Albumin is responsible for 80% of the intravascular colloid osmotic pressure, with 1 gm of albumin holding approximately 18 ml of fluid in the vascular space. Further clinical use established that 25 gm of hyperoncotic albumin is equivalent to 500 ml of plasma (15). It is in this context that albumin has been used in burned patients. All four of the above patients died with shock apparently due to under-resuscitation. The use of large quantities of salt-poor hyperoncotic albumin is the only factor identified as possibly being related to the early mortality. Since albumin is rapidly lost from the intravascular space into the tissues adjoining the burn wound, the use of 25% albumin in the initial resuscitation may be contraindicated for the following reasons. First, albumin does not appear to remain in the vascular space and, therefore, cannot act as a volume expander, as it does in unburned

patients. Second, because it contains little sodium, hyperoncotic salt-poor albumin may not be effective even as a volume replacement fluid. Third, after it shifts into the extravascular space, hyperoncotic albumin may exert a subtraction effect on the vascular space by effecting an obligatory water shift into the interstitial space, which in the lungs may lead to the development of pulmonary infiltrates and edema formation. The net result is inadequate fluid resuscitation, which should elicit an appropriate therapeutic response, realizing that initial fluid calculations serve only as an estimate which must be adjusted to meet individual requirements. If hyperoncotic albumin must be used in the initial resuscitation of a burned patient, it should be suspended in a sufficient volume of saline to produce a solution which is both isotonic and iso-oncotic relative to plasma. Thus, 100 ml of 25% salt-poor albumin should be added to 400 ml of physiologic saline or balanced electrolyte solution if it is to be given as a component of the resuscitation fluids for burned patients.

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